Small Cell Lung Cancer in Never Smokers

Report of Two Cases

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Small cell lung cancer (SCLC) histology in never smokers has been described rarely in the United States.[1] Not surprisingly, the risk factors for lung cancer in never smokers usually pertain to non-small cell histology, with very little data reported on the oncogenesis of SCLC in never smokers. We present two cases of SCLC with a history of never smoking.

CASE 1

A 47-year-old nonsmoker was diagnosed with SCLC metastatic to mediastinum and right supraclavicular lymph nodes. Smoking history was insignificant with only 40 cigars consumed during his lifetime; however, secondhand smoke (SHS) exposure occurred over a 2-year period during employment as a bartender. Positron emission tomography/computed tomography (CT) scan showed a right upper lobe primary tumor nodule, and right hilar, subcarinal, and right supraclavicular adenopathy. Excisional biopsy of the right supraclavicular mass revealed a poorly differentiated neuroendocrine tumor consistent with SCLC histology. Immunohistochemical stains were positive for chromogranin, synaptophysin, thyroid transcription factor-1 (TTF-1), and cell adhesion molecule 5.2 (CAM 5.2) and were negative for CK7, CK20, cytokeratins, and CD99. Chest radiation concurrent with cisplatin and etoposide was initiated, followed by prophylactic cranial irradiation.

Fifteen months later, restaging CT scan revealed an enlarged left supraclavicular node. After excisional lymph node biopsy, immunohistochemical analysis confirmed SCLC with positive staining for cytokeratin AE1 and AE3 and diffusely positive staining for synaptophysin and TTF-1. No mutation in the epidermal growth factor receptor (EGFR) was detected. He was started on two cycles of cisplatin and etoposide and concurrent radiation to the left supraclavicular area followed by two cycles of oral adjuvant topotecan, which resulted in a complete response currently lasting 6 months from the time of recurrence.

CASE 2

An 80-year-old woman with no history of tobacco use was diagnosed with limited stage SCLC. Treatment history was significant for stage 2 breast cancer (T2, N0, estrogen receptor (ER) and progesterone receptor (PR) positive) 24 years before diagnosis and primary biliary cirrhosis 11 years before diagnosis. Breast cancer was treated with modified radical mastectomy and 5 years of adjuvant tamoxifen. A history of SHS exposure was reported over a 25-year period of employment as a secretary. A CT scan showed a 4.6 × 5.1 × 4.6 cm mass in the aortopulmonary window encasing the left pulmonary artery, a 1.9-cm subcarinal lymph node, and a mass in the left upper lobe of the lung measuring 2.5 × 2.1 cm with suspicious regional lymphangitic spread. Bronchoscopic evaluation with biopsy of an endobronchial lesion revealed poorly differentiated neuroendocrine cancer consistent with small cell carcinoma. Immunohistochemical stains were positive for CK7, MOC31, neuron specific enolase (NSE), synaptophysin, and CD56 and were negative for CK20, TTF-1, chromogranin CD57, and p53. Ki-67 marked greater than 90% of nuclei. These morphologic and immunohistochemical profiles were consistent with small cell carcinoma.

The patient successfully completed the radiation and four cycles of concurrent carboplatin and etoposide, resulting in a partial response with a residual tumor measuring 2.4 × 2.3 cm. The patient is currently on surveillance, 4 months after last therapy.

DISCUSSION

SHS exposure has been implicated in the pathogenesis of both small cell and non-small cell variants of lung cancer.[2] Although the causal link between SHS exposure and lung cancer development is well established, it is not possible to accurately estimate the risk for developing lung cancer consequent to SHS exposure.

Several studies have implicated a variety of oncogenes and tumor suppressor genes in the oncogenesis of SCLC, including myc, EGFR, c-raf, c-fms, retinoblastoma, and p53. N-*myc* mutation has been strongly associated with malignancies with neuroendocrine properties, including SCLC.[3] This

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finding is consistent with both of our cases, which showed neuroendocrine features. EGFR mutation, though more common in non-small cell lung cancer, also occurs in SCLC. This mutation was not detected in case 1 and not tested in case 2. In another case report, however, EGFR-positive SCLC was documented in a 72-year-old female nonsmoker.[4] Interestingly, gefitinib was capable of inhibiting EGFR signaling in SCLC cell lines that express the receptor even at low levels. This suggests that EGFR tyrosine kinase inhibitors could be a novel treatment option for a subset of SCLC tumors that express functional or mutated EGFR. In another report, two cases of SCLCs in never smokers tested positive for EGFR mutations.[5] The occurrence of EGFR mutations in SCLC patients who have never smoked should be evaluated and warrants further study.

In addition, there has been cases reported of the occurrence of SCLC in patients with scleroderma who were never smokers, leading to a positive association between SCLC and interstitial pneumonitis because of scleroderma.[6]

In conclusion, sporadic cases of SCLC in never smokers should be reported with analysis of potential risk factors and tissue for elucidation of the oncogenesis of this unique pathology.

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